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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/740,266	12/18/2003	Christian Auclair	1417-03	2270

35811 7590 08/29/2008

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EXAMINER	
FETTEROLF, BRANDON J	
ART UNIT	PAPER NUMBER
1642	
MAIL DATE	DELIVERY MODE
08/29/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/740,266	AUCLAIR ET AL.	
	Examiner	Art Unit	
	BRANDON J. FETTEROLF	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 May 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *55-69* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *55-69* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *8/07/2008*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☒ Other: *Exhibit I*.

DETAILED ACTION

Response to the Amendment

The Amendment filed on 5/30/2008 in response to the previous Non-Final Office Action (11/30/2007) is acknowledged and has been entered.

Claims 55-69 are currently pending and under consideration.

Information Disclosure Statement

The Information Disclosure Statement filed on 8/07/2008 is acknowledged. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner. A signed copy of the IDS is attached hereto.

Rejections Withdrawn:

The rejection of Claims 43-47 and 50-54 under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treating B16F10 murine melanoma tumor cells in a patient comprising administering a therapeutically effective amount of a composition comprising a cDNA of a zyxin gene (see the declaration of Celine Bouquet), does not reasonably provide enablement for a method of treating hepatocarcinoma, mesenchymal tumors, neuroectodermal cancer, Ewing's sarcoma and malignant hemopathies cancer in a patient comprising administering a therapeutically effective amount of a composition comprising cDNA of a zyxin gene, fragment thereof or a complementary sequence has been withdrawn upon careful review and reconsideration of the currently amended claims, the specification, as originally filed, and the two 1.132 Declarations filed on 8/09/2007.

Declarations Reconsidered:

The declaration under 37 CFR 1.132 filed by Celine Bouquet on 8/09/2007 has been carefully reconsidered and found insufficient to overcome the previous rejection of claims 43-47 and 50 under 35 USC, first paragraph, enablement, which will now be applied to new claims 55-69, set forth below, because the Declaration is not commensurate in scope with the claimed invention. As set forth in the Non-Final Office Action, the Examiner recognizes and does not dispute that the

Bouquet Declaration shows that intratumoral injection of a specific recombinant adenovirus, e.g., AdZyxine, coding for the zyxine gene to a nude mouse inoculated with B16F10 murine melanoma cells inhibited tumor volumes by 79% and 73% as compared to controls (page 2, B16F10 tumor). However, the Examiner recognizes that the claims encompass administering any cDNA of a zyxin gene, any fragment thereof or any complementary sequence by any route or vehicle. As such, the specific example of using a recombinant adenovirus, e.g., ADZyxine, harboring a zyxin gene under the control of a cytomegalovirus (CMV) promoter; and further, a specific administration route, e.g., intratumoral does not appear to be commensurate in scope with the claims. Lastly, the Examiner finds it pertinent to point out that Dr. Celine Bouquet appears to have worked on a project based on phenotypic tumoral reversion and actin cytoskeleton network disorganization in tumor cells, wherein the strategy was to transfer the zyxin gene via a recombinant adenovirus. Thus, Dr. Celine Bouquet appears to have prior experience with working with a recombinant adenovirus harboring the zxyin gene.

The declaration under 37 CFR 1.132 filed by Michel Jean Robert Perricaudet on 8/09/2007 has been carefully reconsidered, and found insufficient to overcome the previous rejection of 43-47 and 50 under 35 USC, first paragraph, enablement, which will now be applied to new claims 55-69, set forth below, because the Declaration, while stating that one skilled in gene therapy, as evidenced by the Celine Bouquet declaration, would find the application more than sufficient to practice the claimed invention, does not provide any experimental evidence of success other than reviewing the Celine Bouquet Declaration which was found to be not commensurate in scope with the claimed invention.

New Rejections Necessitated upon Careful Reconsideration.

Claims 55-69 rejected are under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine

screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (Wands, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the nature of the invention, (2) the relative skill of those in the art, (3) the breadth of the claims, (4) the amount or direction or guidance presented, (5) the presence or absence of working examples, (6) the quantity of experimentation necessary, (7) the state of the prior art, and (8) the predictability or unpredictability of the art.

Although the quantity of experimentation alone is not dispositive in a determination of whether the required experimentation is undue, this factor does play a central role. For example, a very limited quantity of experimentation may be undue in a fledgling art that is unpredictable where no guidance or working examples are provided in the specification and prior art, whereas the same amount of experimentation may not be undue when viewed in light of some guidance or a working example or the experimentation required is in a predictable established art. Conversely, a large quantity of experimentation would require a correspondingly greater quantum of guidance, predictability and skill in the art to overcome classification as undue experimentation. In Wands, the determination that undue experimentation was not required to make the claimed invention was based primarily on the nature of the art, and the probability that the required experimentation would result in successfully obtaining the claimed invention. (Wands, 8 USPQ2d 1406) Thus, a combination of factors which, when viewed together, would provide an artisan of ordinary skill in the art with an expectation of successfully obtaining the claimed invention with additional experimentation would preclude the classification of that experimentation as undue. A combination of Wands factors, which provide a very low likelihood of successfully obtaining the claimed invention with additional experimentation, however, would render the additional experimentation undue.

The nature of the invention

The claims encompass a method of treating a particular tumor comprising administering a therapeutically effective amount of a composition comprising a nucleic acid molecule comprising

cDNA of a zyxin gene, a fragment thereof or a complementary sequence thereof. The invention is in a class of invention which the CAFC has characterized as "the unpredictable arts such as chemistry and biology." Mycogen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Fed. Cir. 2001).

Level of skill in the art

The level of skill in the art is deemed to be high, generally that of a PhD or MD.

The breadth of the claims

Applicants broadly claim a method of treating cancers having a zyxin gene expression/abnormality selected from the group consisting of hepatocarcinomas, mesenchymal tumors, neuroectodermal cancer, Ewing's sarcoma and malignant hemopathies associated with chromosomal anomalies or region of 7q34/q35 of a zyxin gene, comprising administering a therapeutically effective amount of a composition comprising a nucleic acid molecule comprising cDNA of a zyxin gene, a fragment thereof or a complementary sequence. Thus, the claims encompass gene therapy using any cDNA of a zyxin gene , any fragment thereof, or complementary sequence via any route or vehicle.

Quantity of experimentation

The quantity of experimentation in the areas of gene therapy for cancer and cancer prevention is extremely large given the unpredictability associated with treating a disease by a method of gene therapy, the lack of correlation of in vitro findings to in vivo success, and the fact that no known cure or preventive regimen is currently available for cancer.

Guidance in the specification and/or Presence of working examples

The specification teaches that zyxin is a protein comprising a LIM domain present in the focal adherence plaques of the fibroblasts and lamellipodia of the superior eukaryote cells, wherein it has been implicated in the requlation of the polymerization of active filaments and has structural and functional properties in common with ActA of Listeria (paragraph 0029 and 0030). The specification further teaches pharmaceutical compositions for the treatment or prevention of

tumoral pathology comprise an active agent which stabilizes the actin network of the cytoskeleton of a cell, wherein the agent includes, but is not limited to, a zyxin protein, a nucleic acid molecule comprising or constituted of the zyxin gene, a fragment thereof or their complementary sequence, or an antisense nucleic acid thereof, a cell or a set of cells over expressing the zyxin gene or a protein coded for a fragment thereof or an inhibitor of cofilin (page 9, paragraph 0036). With regards to the pharmaceutical composition comprising a nucleic acid molecule of the zyxin gene, fragment thereof or complementary sequence, the specification teaches that pharmaceutical composition preferably comprises a vector of intracellular transport including, but not limited to, recombinant adenovirus associated virus (AAV), recombinant baculovirus or retrovirus, and especially preferably a vector of recombinatn lentivirus (paragraphs 0050-0051). In particular, the specification teaches construction of a pLNCX ADA (adaptor) zyxin vector which codes for human zyxin under the direct influence of pCMV (cytomegalovirus) (paragraphs 0074-0078). Moreover, the specification provides examples showing that expression of zyxin EWS-FLI cell lines reduce the tumorigenicity of the tumor cells in nude mice (paragraph 0099, Table 1). Thus, while the specification clearly teaches the production of a pLNCX ADA (adaptor) zyxin vector which codes for human zyxin, and further, that the expression of human zyxin in EWS-FLI cell lines reduce the tumorigenicity of the tumor cells in nude mice, the specification does not appear to set forth the zyxin gene which was used in the vector and appears to be silent on the in-vivo efficacy of any nucleic acid molecule comprising cDNA of a zyxin gene, any fragment thereof or any complementary sequence, e.g. administration of the nucleic acid. Similarly, the specification does not appear to set forth what fragment of a cDNA of a zyxin gene or complementary sequence would have this result. Moreover, the specification does not show any success in treating a disease by using a pharmaceutical composition comprising a nucleic acid molecule comprising cDNA of a zyxin gene, a fragment thereof or a complementary sequence. In other words, the specification does not contain any teachings that address the ability of the composition to treat a human subject or even its ability to work *in vivo*. Specifically, the specification has not taught an appropriate tested dose, the amount of a nucleic acid molecule comprising cDNA of a zyxin gene, a fragment thereof or a complementary sequence necessary for successful treatment, the number of cells to be treated, the number of times the treatment needs to be administered or the most appropriate route of administration. Therefore, one cannot extrapolate the teachings of the specification to the scope of the claims because the claims are drawn to a

pharmaceutical composition comprising a nucleic acid molecule comprising cDNA of a zyxin gene, a fragment thereof or a complementary sequence, and applicant has not enabled the pharmaceutical composition because it has not been shown that these polynucleotides are capable of functioning as to that which is being disclosed. Therefore, coupled with the unpredictability associated with using polynucleotides for the treatment or prevention of cancer, as underscored by the prior art below, the criticality of providing workable examples in an unpredictable art, such as gene therapy and/or cancer therapy, is required for the practice of the instant invention.

The unpredictability of the art and the state of the prior art

The state of the art at the time of filing was such that one of skill could recognize that reference to a zyxin gene encompasses a variety of different species, including but not limited to, Homo sapiens, Mus musculus, Caenorhabditis elegans, Gallus gallus, Rattus norvegicus and Drosophila melanogaster (see Exhibit I). However, the state of art appears to be silent on teh use of these genes with regards to treating cancers in gene therapy.

With regards to gene therapy, the state of the art at the time of filing was such that one of skill could recognize the unpredictability of treating a disease by a method of gene therapy. Gene therapy using administration of recombinant nucleic acids involving *in vivo* or *ex vivo* methods had not seen any success despite a great deal of work and resources. Several reviews in the art show that difficulties with vector selection, mode of delivery and persistence of predictable and effective levels of expression of the protein, created technical barriers to the practice of gene therapy methods. Verma et al states that, "[t]he Achilles heel of gene therapy is gene delivery…", and that, "most of the approaches suffer from poor efficiency of delivery and transient expression of the gene" (Verma et al. (1997) Nature Volume 389, page 239, column 3, paragraph 2, *of record*). Marshall concurs, stating that, "difficulties in getting genes transferred efficiently to target cells- and getting them expressed-remain a nagging problem for the entire field", and that "many problems must be solved before gene therapy will be useful for more than the rare application" (Marshall (1995) Science, Volume 269, page 1054, column 3, paragraph 2, and page 1055, column 1, *of record*). Numerous factors complicate the gene therapy art which have not been shown to be overcome by routine experimentation. Eck et al. (Goodman & Gilman's The Pharmacological Basis of Therapeutics (1996), 9th Edition, Chapter 5, McGraw-Hill, NY, *of record*) explains, "the delivery of exogenous

DNA and its processing by target cells requires the introduction of new pharmakinetic paradigms beyond those that describe the conventional medicines in use today". Eck et al teaches that with *in vivo* gene transfer, one must account for the fate of the DNA vector itself (volume of distribution, rate of clearance into the tissues, etc.), the *in vivo* consequences of altered gene expression and protein function, the fraction taken up by the target cell population, the trafficking of the genetic material within cellular organelles, the rate of degradation of the DNA, the level of mRNA produced, the stability of the mRNA produced, the amount and stability of the protein produced, and the protein's compartmentalization within the cell or its secretory fat, once produced. These factors differ dramatically based on the vector used, the protein being produced and the disease being treated (see Eck et al, bridging pages 81-82). Also among the many factors that the art teaches affect efficient gene delivery and sustained gene expression are, immune responses and the identity of the promoter used to drive gene expression. Verma et al teaches, in reference to *ex vivo* methods, that weak promoters produce only low levels of therapeutically effective protein, and that only by using appropriate enhancer-promoter combinations can sustained levels of therapeutically effective protein be achieved (Verma et al, *supra*, page 240, column 2). Verma et al further warns that, "…the search for such combinations is a case of trial error for a given cell type" (Verma et al, *supra*, page 240, bridging sentence of columns 2-3). The state of the art is such that no correlation exists between successful expression of a gene and a therapeutic result (Ross et al, Human Gene Therapy,1996, Volume 7, pages 1781-1790, *of record*, see page 1789, column 1, first paragraph). Thus, the art at the time at the time of filing clearly establishes that expectation for achieving a desired therapeutic effect in vivo by expressing a therapeutic gene using any of the expression constructs known in the art was extremely low.

More recently, Rubanyi (Mol. Aspects Med. (2001) 22:113-142, *of record*) teaches that the problems described above remain unresolved. Rubanyi states, "[a]lthough theoretical advantages of [human gene therapy] are undisputable, so far [human gene therapy] has not delivered the promised results: convincing clinical efficacy could not be demonstrated yet in most of the trials conducted so far…" (page 113, paragraph 1). Among the technical hurdles that Rubanyi teaches remain to be overcome are problems with gene delivery vectors and improvement in gene expression control systems (see "3. Technical hurdles to be overcome in the future", beginning on page 116 and continued through page 125). Furthermore, Juengst (British Medical Journal (2003) Volume 326,

pages 1410-1411, *of record*) teaches the unpredictable nature of gene therapy and that a few of the apparent successes actually developed T cell-acute lymphoblastic leukemia due to insertional mutagenesis at or near the LMO-2 gene causing altered gene expression. Similarly, Orkin et al (Report and Recommendations of the Panel to Assess the NIH investment in Research on Gene Therapy, 1995) state that "while the expectations and the promise of gene therapy are great, clinical efficacy has not been definitively demonstrated at this time in any gene therapy protocol, despite anecdotal claims of successful therapy and the initiation of more than 100 Recombinant DNA Advisory Committee (RAC)-approved protocols" and further teach that significant problems remain in all basic aspects of gene therapy. Culver et al (TIG, 1994, 10:174-178) reviewing gene therapy for cancer, conclude that the "primary factor hampering the widespread application of gene therapy to human disease is the lack of an efficient method for delivering genes *in situ*, and developing strategies to deliver genes to a sufficient number of tumor cells to induce complete tumor regression or restore genetic health remains a challenge " (p. 178). Further, Orkin et al reports major difficulties at the basic level include shortcomings in all current gene transfer vectors and an inadequate understanding of the biological interaction of these vectors with the host. (see page 1). In addition, the research community, as reported by Nature Biotechnology, 1997, 15:815, has responded to the issues raised in the Orkin Report drawn to vector based delivery systems, that is the critical steps of delivery of a gene to the right cell and the subsequent maintenance of gene expression, since it is now widely appreciated that the natural tropism of a virus, while advantageous to its own replication cycle is not always optimal for a gene delivery protocol and a number of laboratories have explored methods to redirect the targeting that has evolved to ensure viral infectivity in ways that may be more suitable to the aims of gene therapy and concludes that this return to first principles should help to continue to move gene therapy in the direction of its largest and most important ambitions (p. 815). Clearly, at the time the invention was made, gene therapy was an unpredictable art. This unpredictability was further clarified by the tragic setback, in 2002, in the most celebrated clinical trial drawn to the treatment of SCID in children wherein gene therapy led to cancer because of insertional mutagenesis (see Cheek [Nature, 2002, 420:116-118]) wherein the NIH urged all investigators conducting retroviral-mediated gene transfer in hematopoietic cells to discontinue enrollment and administration of the experimental agent until new data are available (see Attached Letter of January 14, 2003, Exhibit 1). Thus, the art has demonstrated that a large amount of

experimentation has already been performed without demonstrating successful gene therapy methods for treatment of disease.

With regards to preventing cancer, those of skill in the art recognize that reasonable guidance with respect to preventing any cancer relies on quantitative analysis from defined populations which have been successfully pre-screened and are predisposed to particular types of cancer. This type of data might be derived from widespread genetic analysis, cancer clusters, or family histories. The essential element towards the validation of a preventive therapeutic is the ability to test the drug on subjects monitored in advance of clinical cancer and *link* those results with subsequent histological confirmation of the presence or absence of disease. This irrefutable link between antecedent drug and subsequent knowledge of the prevention of the disease is the essence of a valid preventive agent. Further, a preventive administration also must assume that the therapeutic will be safe and tolerable for anyone susceptible to the disease. Further, treatment of cancer in general is at most unpredictable, as underscored by Gura (Science, v278, 1997, pp.1041-1042) who discusses the potential shortcomings of potential anti-cancer agents including extrapolating from in-vitro to in-vivo protocols, the problems of drug testing in knockout mice, and problems associated with clonogenic assays. Indeed, since formal screening began in 1955, thousands of drugs have shown activity in either cell or animal models, but only 39 that are used exclusively for chemotherapy, as opposed to supportive care, have won approval from the FDA (page 1041, 1st column) wherein the fundamental problem in drug discovery for cancer is that the model systems are not predictive.

Conclusion

Thus given the broad claims in an art whose nature is identified as unpredictable, the unpredictability of that art, the large quantity of research required to define these unpredictable variables, the lack of guidance provided in the specification, the presence of a working example which does not address the issue of the efficacy of the control and the negative teachings in the prior art balanced only against the high skill level in the art, it is the position of the examiner that it would require undue experimentation for one of skill in the art to perform the method of the claim as written.

Note: In order to expedite prosecution, the Examiner would like to address Applicants remarks to the previous rejection as they relate to the instant rejection. In response to the previous rejection, Applicants contend that the breadth of the claims are fully enabled as to all subject cancers treated. For example, Applicants submit that the claims have been amended to include only those cancers that have been shown to have zyxin gene expression/abnormality. Thus, Applicants submit that the methods are no longer drawn to the treatment of any and/or all heptocarcionmas, mesenchymal tmors, neuroectodermal cancers, ect. Moreover, Applicants contend that the Examiners points to the complexity of the art, and alleged failures by others in practicing certain treatment methods (e.g., gene therapies) to support the analysis that reduction to practice of APplicants' methods would require undue experimentation. However, Applicants submit that the fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. See MPEP 2164.01. In this light, Applicants submit that the present specification teaches how to make and use the invention without undue experimentation. Applicants further submit that the previously provided Declarations by Drs. Celine Bouquet and Michel Jean Robert Perricaudet provides evidence supporting that one of ordinary skill in the art, at the priority date of the present application, would not have had difficulty in treating at least two distinct forms of cancer in vivo with the pharmaceutical compositions of the present application. For example, Applicants assert that the Declarations describe the replication of the antitumor effects of Adenoviral constructs comprising an E1-E3 deficent Adenovirus harboring a zyxin gene under the contrl of a cytomegalovirus (CMV) promoter in mice (see Specification as originally filed, page 13, paragraph 0051-0052). In particular, Applicants assert that the Dr. Bouquet Declaration shows the reduction of two distinct tumors, B16F10 and NIH 3T3 EF cell line, in vivo in accepted and known cancer mice models which provides support that the claims were enabled as of the date of the filing and in particular for the new claims presented herein. With regards to the NIH 3T3 EF cell line, Applicants contend that the NIH 3t3 EF cell line is an extremely well known and tested cell line which has been in continuous use as a fibroblost tumor cell since the late 1960's. Hence Applicants contend that the in vitro results show in the Specification at pages 35-38, evidenced by the in vivo results accordingly obtained by Dr. Bouquet with respect to suppression of the EWS-FLI-1 oncogenicity and melanoma tumors in mice establish that the specification provides enablement for the full scope of the claims herein. In addition, in contrast to the Examiner's

assertions that no in vivo examples were set forth in the specification, Applicants contend that the specification provides in vivo results in mice describing the protective effects of over expression of zyxin and the induction of a loss of malignant phenotype in the nude mouse. Thus, Applicants submit that given the guidance and working examples in the Specification as filed, Dr. Bouquet was able to independently replicate the effectiveness of the exemplified pharmaceutical compositions against two distinct tumors. Furthermore, with regards to the Examiner's allegations on page 10 of the Office action, Applicants submit that "[I]t is not necessary to specify the dosage or method of use if it is known to one skilled in the art that such information cold be obtained without undue experimentation. If one skilled in the art, based on knowledge of compounds having similar physiological or biological activity, would be able to discern an appropriate dosage or method of use without undue experimentation, this would be sufficient to satisfy 35 USC 112, first paragraph. See MPEP 2164.01 (c). In the instant case, Applicants contend that prior to the time of filing the present application there were many completed and ongoing cancer gene therapy trials involving viral constructs encoding a therapeutic gene targeting one or more cancers. As such, Applicants assert that the ability to formulate specific pharmaceutical compositions and use them in the claimed methods, including phase I clinical trials, was well established at the time of filing, and a matter of routine experimentation. Moreover, Applicants contend that the selection of viral vectors, their promotors and methods of administration are provided in detail in the specification (for example, the generation of retroviral stocks having a human zyxin gene inserted and under the control of a CMV promoter is described in detail in the material and method section of the application on pages 17-23. Methods for determining the expression of zyxin in various cell types can also be found in the material and method section of the application.). Lastly, Applicants assert that the literature presented by the Examiner to support the contention that the method of treating disease with gene therapy was unpredictable at the time of filing were published prior to the filing of the present application when gene therapy was a relatively nascent technology. For example, Applicants contend that Verma discloses that "thus far, the problem has been inability to deliver genes efficiently and to obtain sustained expression. However, Applicants assert that issues relating to delivery and sustained expression has been largely overcome by intratumoral administration rather than systemic administration for example by intravenous routes. See for examples, Khuri et al. A controlled trial of intratumoral ONYX-015, a selectively replicating adenovirus, in combination with

cisplatil and 5-fluorouracil in patients with recurrent head and neck cancer." Nature Medicine (2000), 6(8): 879-885. In addition, Applicants contend that the Rubanyi publication relates not toe the problems identified by Veram et al., Ross and Eck et al., but provides numerous examples where obstacles to gene delivery have been overcome. For example,, Applicants contend that Rubanyi states on pga 122, "A variety of physical gene delivery methods have been introduced to achieve better local tissue targeting of vectors. An example of the effective physical targeting is catheter-mediated gene transfer to various regions of the circulation…." Applicants further contend that the several articles published prior to the date of the filing the present application that discuss advancement in the treatment of incurable cancers using viral mediated gene therapy. For examples, Khuri et al. describes the successful treatment of squamous cell carcinoma using Adenoviral vector ONYX-015 which, line the ADZyxine viral vector sued by Dr. Bouquet, lacks E1 and E3 gene regions, in particular the E1B gene. As such, methods described in the ONYX-015 trials are standardized Adenoviral dosages and can be obtained using routine experimentation. Hence, Applicants contend that the patient dosages, the amount of nucleic acid used per treatment, the patient criteria, routes of administration, or the number of tumors the treatment needs to be administered can be derived using routine experimentation and are taught in several phase I and II clinical trials using viral constructs which are exemplified in the present invention.

These arguments have been carefully considered, but are not found persuasive.

In response to Applicants amendments, the Examiner acknowledges and appreciates Applicants amendments to the claims so that the claims are drawn to only those cancers that have been shown to have zyxin gene expression/abnormality. However, the Examiner recognizes that the amendment does not appear to satisfy the requirements set forth in 35 USC 112, 1st paragraph for the reasons set forth above and for the reasons set forth below. In particular, the claims encompass a method of treating these cancers comprising administering cDNA of a zyxin gene, fragment thereof, or complementary sequence thereof. Thus, the claims broadly encompass administration of any cDNA of a zyxin gene, any fragment thereof, or any complementary sequence thereof via any route or vehicle. However, the specification does not appear to set forth what zyxin gene was used in the production of the vector and appears to be silent on the in-vivo efficacy of any nucleic acid molecule comprising any cDNA of a zyxin gene, any fragment thereof or any complementary sequence. Similarly, the specification does not appear to set forth what fragment of a

cDNA of a zyxin gene or complementary sequence would have this result, e.g., effective at treating cancer. Moreover, the specification does not show any success in treating a disease by using a pharmaceutical composition comprising a nucleic acid molecule comprising cDNA of a zyxin gene, a fragment thereof or a complementary sequence. In other words, the specification does not contain any teachings that address the ability of the composition to treat a human subject or even its ability to work *in vivo*. Specifically, the specification has not taught an appropriate tested dose, the amount of a nucleic acid molecule comprising cDNA of a zyxin gene, a fragment thereof or a complementary sequence necessary for successful treatment, the number of cells to be treated, the number of times the treatment needs to be administered or the most appropriate route of administration. Therefore, one cannot extrapolate the teachings of the specification to the scope of the claims because the claims are drawn to a pharmaceutical composition comprising a nucleic acid molecule comprising cDNA of a zyxin gene, a fragment thereof or a complementary sequence, and applicant has not enabled the pharmaceutical composition because it has not been shown that these polynucleotides are capable of functioning as to that which is being disclosed. Moreover, the Examiner acknowledges and does not dispute Applicants contention that the fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. However, the Examiner recognizes that Applicants have not provided any evidence to suggest that complex experimentation is typical, and therefore, not undue in the area's of gene therapy. As noted above, the Examiner recognizes that the state of the art, at the time the invention was made, was such that one of skill could recognize the unpredictability of treating a disease by a method of gene therapy, wherein difficulties with vector selection, mode of delivery and persistence of predictable and effective levels of expression of the protein, created technical barriers to the practice of gene therapy methods. Therefore, coupled with the unpredictability associated with using polynucleotides for the treatment of cancer, as underscored by the prior art above, the criticality of providing workable examples in an unpredictable art, such as gene therapy and/or cancer therapy, is required for the practice of the instant invention. With regards to Applicants assertions that the two Declaration provide evidence of an enabling disclosure, the Examiner acknowledges and has reconsidered the two Declarations, and does not dispute that the Bouquet Declaration shows that intratumoral injection of a specific recombinant adenovirus, e.g., AdZyxine, coding for the zyxine gene to a nude mouse inoculated with B16F10 murine melanoma cells

inhibited tumor volumes by 79% and 73% as compared to controls (page 2, B16F10 tumor). However, the Examiner recognizes that the examples provided in the Declaration do not appear to be commensurate in scope with the claimed invention. For example, the Examiner recognizes that the claims encompass administering any cDNA of a zyxin gene, any fragment thereof or any complementary sequence by any route or vehicle. As such, the specific example of using a recombinant adenovirus, e.g., ADZyxine, harboring a zyxin gene under the control of a cytomegalovirus (CMV) promoter; and further, a specific administration route, e.g., intratumoral does not appear to be commensurate in scope with the claims. In addition, it is interesting to note that the Declaration does not appear to use the vector construct taught in the specification which comprises recombinant lentivirus type (page 18, paragraph 0074), but instead uses a specific recombinant adenovirus not mentioned in any part of the specification. Moreover, it is also noted that intratumoral injection is not found in any part of the specification as originally filed. With regards to the NIH 3T3 EF cell line, the Examiner acknowledges and does not dispute Applicants assertions that the NIH 3T3 EF cell line is an extremely well known and tested cell line. However, in view of the unpredictability of treating a disease by a method of gene therapy, it would be unpredictable to draw the conclusion that in vitro results are predictive of in vivo results. As such, the in vitro example of treating the NIH 3T3 EF cell line as presented by Dr. Bouquet does not appear to be predictive of in vivo results. This same response can be applied to Applicants assertion that the specification teaches in vivo results wherein overexpression of zyxin in cells transfected, ex vivo, with zyxin provided a protective effect and the induction of a loss of malignant phenotype in the nude mouse. In particular, the ex vivo transfection of a cell and subsequent administration of said cell does not appear to be commensurate in scope with gene therapy which requires different considerations, such as an appropriate tested dose, the amount of a nucleic acid molecule comprising cDNA of a zyxin gene, a fragment thereof or a complementary sequence necessary for successful treatment, the number of cells to be treated, the number of times the treatment needs to be administered or the most appropriate route of administration. Regarding Applicants arguments pertaining to what is known in the art, the Examiner acknowledges and does not dispute Applicants assertions that "[I]t is not necessary to specify the dosage or method of use if it is known to one skilled in the art that such information cold be obtained without undue experimentation. If one skilled in the art, based on knowledge of compounds having similar physiological or biological

activity, would be able to discern an appropriate dosage or method of use without undue experimentation, this would be sufficient to satisfy 35 USC 112, first paragraph." See MPEP 2164.01 (c). However, the Examiner recognizes that this situation does not appear to apply to methods of gene therapy. For example, Rubanyi et al. (of record), on page 127, teaches

> "[T]hat the field of gene therapy for cancer now has the experience of numerous clinical trial data to assess the efficacy of both the agents and the vectors which have been used so far. However, the available technology (e.g., potency of therapeutic genes and efficacy of gene delivery vectors) are far from optimal to achieve the desired benefits in the filed of solid tumors and their metastasis. The available data suggest that the problems with cancer gene therapy involve primarily the gene delivery technology rather than the choice of the therapeutic agents.
>
> Although there are numerous gene therapy clinical trials in the cancer field reaching the Phase II and Phase III stages with both viral (table 4) and non-viral vectors (Table 5), they invariably use local, intratumoral delivery routes, and not the more optimal systemic delivery route yet, which would allow treatment of not only the primary tumor buts also its metastasis. The main reason for this is the fact that none of the existing vectors allow effective and selective gene delivery and gene expression in the tumor tissue. In order to accomplish this goal, significant technical hurdles (e.g. bystander effect, conditionally replicating viruses, vector targeting, ect.) need to be overcome in the future."

In light of this, it does not appear that formulating a pharmaceutical composition, in view of the state of the art, for use in successful gene therapy is as trivial as asserted by Applicants. In the instant case, the Examiner reiterates the unpredictability of treating a disease using gene therapy recognized by those of skill in the art. With regards to Applicants arguments pertaining to the literature cited above, the Examiner acknowledges and does not dispute that many of the articles cited above where published a number of years prior to the filing date of the present invention. However, the Examiner recognizes that, as evidenced by Rubanyi et al. which was filed the same year as the instant application, many of problems described in the earlier published articles remain unresolved. Thus, while the Examiner acknowledges and does not dispute Applicants arguments that there have been successes in the field of gene therapy (for example, Kunthi et al), the Examiner

recognizes that success using a specific vector, a specific gene and a specific route of administration does not appear to extend to the success of gene therapy in general.

Therefore, No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to BRANDON J. FETTEROLF whose telephone number is (571)272-2919. The examiner can normally be reached on Monday through Friday from 7:30 to 4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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